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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,034	08/16/2000	Toshiyuki Yoneda	BEAR-006	3757

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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,034	YONEDA ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-24* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Introduction

1. It is not clear whether the previous Office action was a final rejection or not but if it was then the finality is hereby withdrawn. The instant Office action maintains the rejection of claims 1-3, 5, 8, 12, 13 and 16 as anticipated by Cheng et al. under 35 USC 102(b); the rejection of claim 4 as anticipated by Cheng et al. is withdrawn since they teach 11-amino acid peptides and 11 is not "about 15". The rejection under 35 USC 112, second paragraph is hereby withdrawn. The rejection of claims 1-5, 8 and 12-16 as obvious over Cheng et al. in view of Cerny et al. under 35 USC 103(a) is maintained. The rejection of claims 1-5, 7-9, 12, 13 and 16 as obvious over Cheng et al. in view of Cerny et al. and further in view of Rowe et al. is hereby withdrawn.

This Office action contains some new grounds of rejection. Examiner apologizes for any inconvenience this may cause applicants but the issues raised in the application dictate these rejections. The new grounds of rejection include inadequate written description and enablement under 35 USC 112, first paragraph and a reinstated rejection under 35 USC 102(b)/103 over Rowe (WO 99/60017) and 35 USC 102(e)/103 over Rowe (US 6,673,900). Also, a new rejection under 35 USC 103(a) over Rowe in view of Cerny et al. is imposed. Finally, a new obviousness-type double patenting rejection over 09/812,485 is imposed.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 4, 5, 17 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides wherein the integrin binding motif is RGD, does not reasonably provide enablement for peptides wherein the integrin binding motif is other than RGD. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be very large because one of skill in the art would first have to determine what constitutes an integrin binding motif, then determine whether it enhances bone growth. The specification provides no direction or guidance as to what any other integrin binding motif might be or what properties it might have. There are no working examples of another integrin binding motif besides RGD. The nature of the invention is a peptide for use in enhancing bone growth in humans. The state of the prior art is such that one or two other integrin binding motifs are known but they have not been characterized as to their usefulness for enhancing bone growth. The relative skill of those in the art is high. The predictability of the art is considered to be low. Nobody knows what properties proteins might have without testing them, it is known to be an empirical art. Finally, the breadth of the claims is unknown because the class of integrin binding motifs is not fully characterized.

Thus, in view of the large amount of experimentation required, the absence of guidance or direction as to what peptides to test and the unpredictability of the art the conclusion of undue experimentation is dictated and therefore the above claims are not enabled.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

4. Claims 1-5, 8, 12-18 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The above claims are directed to peptides consisting of about 10-50 or, more narrowly, 15-35, amino acids containing an integrin binding motif and having the biological property of enhancing bone growth. The specification, however, only provides a few representative examples, SEQ ID Nos. 43, 44, 45 and 47, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the four examples except for the presence of RGD. While it is clear that the peptide binds to integrin via the RGD site it is also clear that mere binding to integrin does not provide the requisite biological activity. The specification also fails to describe additional representative species of integrin binding motifs by any identifying structural characteristics or properties, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants' written description of the claimed invention is insufficient to show that they were in possession of the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-5, 7-9, 12, 13 and 16-22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rowe (WO 99/60017).

Rowe teaches a protein (SEQ ID No. 2) comprising an amino acid sequence identical to SEQ ID No. 47; SEQ ID No. 47 is at positions 147-169 of Rowe's SEQ ID No. 2. The disclosed biological activity is enhancing bone growth (p. 1, last paragraph and claims 24, 39 and 40). The amino acid sequence is contiguous with the RGD sequence in naturally occurring protein matrix extracellular phospohglycoprotein (human protein-see abstract and p. 4 of the sequence listing), and the peptide is

biologically active in promoting phosphate metabolism and bone growth (claims 24, 39 and 40). The phosphatonin polypeptide positively regulates bone mineralization which is a pre-requisite for bone growth, p. 43, lines 1-3 and p. 49, lines 22-26) and may be used to treat impaired bone formation and osteomalacia (p. 49, lines 10-11) and wherein the peptide is administered in a formulation comprising a therapeutically effective amount with a carrier (paragraph bridging pages 86 and 87).

Applicants have previously argued that Rowe does not teach peptides of 10-50 or 15-35 amino acids and, therefore, does not anticipate these claims. Attention is directed to pages 34 and 35 where polypeptide fragments are discussed, Rowe specifically exemplifies 21 fragments, including 141-160 and 161-180; Rowe discusses fragment size in the paragraph bridging pages 34 and 35, including 20, 30, 40 and 50 amino acid fragments which may be larger or smaller. The disclosure also discusses which fragments would be desirable to use, thy include flexible regions, substrate binding regions and turn regions (page 35, second paragraph). Page 77 contains specific guidance to select a fragment comprising RGD, see the first two lines. Importantly, Rowe states, "It is highly probably that this part of the phosphatonin is involved in receptor and/or bone mineral matrix interactions. . . . 4. bone and dental mineral matrix interactions and regulation of mineral deposition via nucleation." This is considered to be enough disclosure to place all fragments containing RGD in possession of the public, including the fragment from 147-169, the claimed SEQ ID No. 47.

Alternatively, should the above teachings not anticipate the claims, it would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the clear teachings of the references and select any of the fragments containing RGD in possession of the public, including the fragment from 147-169, the claimed SEQ ID No. 47.

8. Claims 1-5, 7-9, 12, 13 and 16-22 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rowe (US 6,673,900).

The logic of this rejection is exactly the same as the previous one over Rowe (WO 99/60017). US Patent 6,673,900 originated as US Patent Application 09/434,185, filed November 4, 1999. Thus, the reference qualifies as prior art under 35 USC 102(e).

9. Claims 1-5, 8, 12, 13 and 16 are again rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cheng et al.

This rejection was explained in the previous Office action. Since the instant claims are not limited to non-cyclic, i.e., linear, peptides, the rejection stands.

Claim Rejections - 35 USC § 103

10. Claims 1-5, 8 and 12-16 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. in view of Cerny et al.

This rejection was explained in the previous Office action. Applicants argued that this rejection should fail since Cheng et al. is not applicable as a reference. As this is not the case, this rejection is maintained.

11. Claims 14, 15, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowe (both WO 99/60017 and US Patent 6,673,900) in view of Cerny et al.

The teachings of the references have been previously provided. It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the peptide of Rowe as a mouthwash or a toothpaste in view of Rowe's statements on page 77 about dental implications of phosphatonin and Cerny et al.'s disclosure of an RGD peptide in toothpaste and mouthwash.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 2 and 12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 7 of copending Application No. 09/812,485. Although the conflicting claims are not identical, they are not patentably distinct from each other because the linear and circular peptides are considered variations on a theme since they would be expected to behave similarly.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

14. It is considered that all arguments have been adequately addressed above in the body of the rejections.

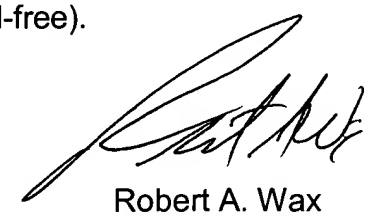
Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653